IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

		Atty. Docket: TOVEY=1A
In re Application of:	)	Conf. No.: 1869
Michael TOVEY	)	Art Unit: 1614
Appln. No.: 09/243,030	)	Examiner: R. Cook
Filed: February 3, 1999	)	Washington, D.C.
For: THERAPEUTIC APPLICATIONS OF HIGH DOSE INTERFERON	)	

DECLARATION

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Randolph Building, Mail Stop Amendments
401 Dulany Street
Alexandria, VA 22314

Sir:

I, the undersigned Michael Tovey, Ph.D., hereby declare and state as follows.

I am Director of the Laboratory of Viral Oncology CNRS UPR9045 at the Institut Andre Lwoff (French National Cancer Institute), and INSERM (French National Institute of Health), Director of Research at CNRS. I am also the named inventor on the present application. My *Curriculum Vitae* is attached hereto as Exhibit A.

In the 1996-97 timeframe, those of ordinary skill in the art understood what was meant by the term "a single dose of interferon", with respect to interferon therapy.

Interferons work by binding to specific high affinity receptors on target cells. A single administration of optimum dosage will saturate those receptors, or at least bind an appropriate number of such receptors. Over a period of time, interferon bearing receptors are down regulated and new binding sites become available for binding to additional interferon. Thus, a "single dose" does not mean a daily dose, but the dose of each administration for optimum effect of that single administration. This is then repeated every several hours as needed.

This is illustrated by the results of a study that show that treatment of patients with recombinant IFN alpha results in a striking decrease in the ability of patients cells to bind IFN. This is observed in all patients within 6 to 12 hours of administration of a single dose of IFN and has been shown to result from a loss of IFN receptors on the surface of cells due "down-regulation" and internalization of IFN receptors (Billard et al, *Blood,* 67:821-826 (1986), a copy of which is attached hereto as Exhibit B). Loss of IFN receptors is accompanied by a resulting loss in the ability of a patient's cells to respond to IFN treatment (Billard et al, *Leuk Res,* 12:11-18 (1988), a copy of which is attached hereto as Exhibit C). IFN receptor expression, and hence sensitivity

to IFN, then recovers again usually after 12 to 24 hours after the initial treatment (Billard et al, *Blood* (1986), *supra*).

When my application refers to "a single dose or multiple or continuous administration of smaller doses to have the same cumulative effect as a single dose" one is referring to multiple or continuous administration over the period of optimum activity of a single dose, i.e., all fairly quickly so as to achieve the optimum saturation of receptors equivalent to that of a single dose. Reference to multiple administration of smaller doses would not be met by administration of a smaller dose once every several hours.

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

10 June 2005.
Date

Michael Tovey
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